REMARKS

The foregoing amendment is being offered to correct typographical errors inadvertently filed with the application. No new matter is presented by this Amendment. Entry of this amendment by the Examiner is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached paper is captioned "**Version with Markings to Show Changes Made**."

Attached hereto are substitute pages showing the marked-up version of the changes made to the specification by the current amendment. The attached papers are captioned "**Substitute Pages**."

Authorization is given to charge payment of any additional fees required, or credit any overpayment, to Deposit Acct. 13-4213. A duplicate of this paper is enclosed for accounting purposes.

Respectfully submitted,

Dated: March 29, 2002

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Version with Markings to Show Changes Made

EXAMPLE 5 **Pharmacokinetics in Rats Following IV Administration of Compound 1**

A sensitive bioassay, based on high affinity binding to MCRs, was used to monitor plasma levels of **Compound 1** in dosed rats. Rats were dosed intravenously with 100 µg/kg of **Compound 1**. A bi-phasic pharmacokinetic profile resulted, as shown in **FIG. 1**.

EXAMPLE 6 **Pre-Formulation Studies for Nasal Delivery**

A series of pre-formulation studies for nasal delivery were conducted. This study shows the stability of the peptide Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH, at a concentration of .825 mg/mL, over a period of twelve weeks, with storage at 40° C.

EXAMPLE 7 **Formulations for Nasal Delivery**

Based on the pre-formulation study of **Example 6**, two formulations were prepared. For the first, the peptide Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH was dissolved in a 0.9% saline solution, pH approximately 6.0, at a concentration of .825 mg per mL of solution (**Nasal Formulation 1**). [In an alternative formulation, Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH was dissolved in a 50 mM citrate, pH approximately 6.0, also at a concentration of .825 mg per mL of solution.]

EXAMPLE 8 **Inhibition of Compound 1 Using Melanocortin Antagonist**

The effect of a nonselective melanocortin antagonist, SHU9119 (Hruby VJ, Lu D, Sharma SD, et al. *J Med Chem* 38:3454-3461 (1995)), Ac-Nle-cyclo(-Asp-His-D-Nal(2')-Arg-Trp-Lys)-NH_2, to inhibit induction of penile erection with **Compound 1** was studied. A group of four Sprague Dawley rats were administered 5 µg/kg of SHU9119 by intravenous administration, and five minutes later 25 or 50 µg/kg of **Compound 1** in **Nasal Formulation 1** was administered by nasal administration. No erections were observed in the rats over the one-half hour observation period. No erections were observed in rats administered a saline control by nasal administration. In control groups, 100% of the rats administered the same dose of **Compound 1** by the same route of administration, but without pre-administration of SHU9119, had observed erections. **FIG. 4** shows the number of penile erections per rat during the initial 30 minute period post-administration; as shown for the 25 µg/kg level, no penile erections were observed with pre-administration of SHU9119.

EXAMPLE 9 **Nasal Administration to Cynomolgus Monkeys**

Nasal Formulation 1 of **Example 6** was administered to cynomolgus monkeys by nasal spray, at a dose of approximately 50 µg per kg of body weight. Compared to intravenous injection of the same dose of Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH, the mean bioavailability of the peptide using **Nasal Formulation 1** was approximately 0.73% ± 0.05. In a related cardiovascular safety study using cynomolgus monkeys with intranasal administration of **Nasal Formulation 1**, an erection lasting approximately one hour was observed in one of four monkeys.

EXAMPLE 10 **Pharmacokinetic Profiles Following Administration to Cynomolgus Monkeys**

A sensitive radioimmunoassay [bioassay, based on high affinity binding to MCRs,] was used to monitor plasma levels of **Compound 1** in cynomolgus monkeys. Monkeys were dosed intravenously with 50 µg/kg of **Compound 1**. A bi-phasic pharmacokinetic profile resulted, as shown in **FIG. 2**. Selected monkeys were intranasally administered 50 µg/kg of **Compound 1** in **Nasal Formulation 1**, and the resulting pharmacokinetic profiles are shown in **FIG. 3**.

EXAMPLE 11 **Nasal Administration Dosing Study in Rats**

In another series of experiments, a dosing study was conducted in rats by nasal administration of from 15 µg per kg of body weight to 1500 µg per kg of body weight, using **Nasal Formulation 1**. Based on penile erectile response behavior, the peptide was efficacious at all dose amounts administered, and particularly from 25 µg/kg to 75 µg/kg, with pharacologic effect observed over the range from 15 µg/kg to 1500 µg/kg. In addition, the response rate and side effects differed significantly from those demonstrated with nasal administration of Melanotan-II. With nasal administration of the peptide of Melanotan-II, the penile erection response was primarily in the 2nd and 3rd ten-minute period, while with **Nasal Formulation 1** the penile erection response was primarily in the 1st and 2nd ten-minute period. Additionally, no adverse side effects were detected at any dosage level with **Nasal Formulation 1**, while adverse side effects were seen with administration of higher doses of the peptide of Melanotan-II. **Table 4** sets forth the comparative data:

0.1 mL of sesame oil, four hours prior to testing. Administration of estradiol benzoate and progesterone induced full sexual receptivity in the female rats. Female rats were placed in bilevel chambers five minutes prior to the introduction of a sexual vigorous male. After females acquired baseline rates of sexual activity, a dose response analysis of **Compound 1** was conducted, with 0, 50, 100 or 200 µg/kg, injected subcutaneously, one minute before each test. Tests were videotaped and score subsequently for appetitive level changing during the five minute period prior to the introduction of the male, lordosis quotients and reflex magnitudes, incidents of solicitation (head-wise orientation and runaway), hops and darts, pacing (level changes per mount), female mounts and defensive responses. **FIG. 6** depicts results, with a between-subjects analysis of variance (ANOVA) of $P < 0.004$. In a second experiment, female rats were administered only estradiol benzoate prior to administration of 0 or 200 µg/kg of **Compound 1** injected subcutaneously. The results are shown in **FIG. 7**. In general, in both experiments the 200 µg/kg dose of **Compound 1** increased the number of solicitations significantly without affecting rates of appetitive level changing, pacing, lordosis, female mounts or rejection responses.

EXAMPLE 14 **Female Sexual Response in Rats**

Female Long-Evans rats as in Example 13 were tested in a unilevel pacing chambers bisected by a [four-hold] four-holed divider, as generally described in Yang L.V. and Clemens L.G., *Physiol Behav* 61:889-894 (1997), for five minutes prior to the introduction of a sexually vigorous male for a thirty-minute test of copulation. As in Example 13, following priming with estradiol benzoate and progesterone, 0, 50, 100 or 200 µg/kg of **Compound 1** was administered subcutaneously one minute before each test, with female animals placed in the unilevel pacing chambers bisected by the four-hole divider through which only the females could pass. Tests were videotaped and scored as in Example 13, with pacing defined as number of exits from and returns to the side with the male; and exist and return latencies following mounts, intromissions or ejaculations. **FIGS. 8 A, 8 B, 8 C** and **8 D** show the results. The 200 µg/kg dose of **Compound 1** increased the number of solicitations, hops and darts, and female mounts significantly compared to controls, but had no effect on lordosis or defensive responding. This dose also increase the ejaculation return latencies, but not the mount or intromission return latencies. This dose had no significant effect on the number of exits or returns made by the females.

Substitute Pages

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0.1 mL of sesame oil, forty-eight hours prior to testing, and progesterone, 500 µg in 0.1 mL of sesame oil, four hours prior to testing. Administration of estradiol benzoate and progesterone induced full sexual receptivity in the female rats. Female rats were placed in bilevel chambers five minutes prior to the introduction of a sexual vigorous male. After females acquired baseline rates of sexual activity, a dose response analysis of **Compound 1** was conducted, with 0, 50, 100 or 200 µg/kg, injected subcutaneously, one minute before each test. Tests were videotaped and score subsequently for appetitive level changing during the five minute period prior to the introduction of the male, lordosis quotients and reflex magnitudes, incidents of solicitation (head-wise orientation and runaway), hops and darts, pacing (level changes per mount), female mounts and defensive responses. **FIG. 6** depicts results, with a between-subjects analysis of variance (ANOVA) of $P < 0.004$. In a second experiment, female rats were administered only estradiol benzoate prior to administration of 0 or 200 µg/kg of **Compound 1** injected subcutaneously. The results are shown in **FIG. 7**. In general, in both experiments the 200 µg/kg dose of **Compound 1** increased the number of solicitations significantly without affecting rates of appetitive level changing, pacing, lordosis, female mounts or rejection responses.

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